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EFFICACY AND SAFETY PROFILE OF EMPAGLIFLOZIN IN PATIENTS WITH METABOLIC SYNDROME

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Abstract

BACKGROUND :

The EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus) trial found that adding empagliflozin, a sodium-glucose co-transporter-2 inhibitor (SGLT-2i), to a standard of care, reduces the relative risk of cardiovascular death by 38%, all-cause mortality by 32%, and hospitalization for heart failure (HHF) by 35% when compared to placebo in patients with type 2 diabetes. (T2D). More than 99 percent of EMPAREG OUTCOME participants had a history of cardiovascular disease.

AIM

The primary objective of the study is to evaluate the safety and efficacy of empagliflozin in patients with Metabolic syndrome.

CONCLUSION

It is too early to compare the perks of empagliflozin to those of other glucose-lowering drugs in routine clinical settings, particularly for patients without a history of cardiovascular disease. In addition, although safety data for empagliflozin and other SGLT-2i have been reported in substantial RCTs, evidence regarding the safety of these drugs is still accumulating because RCTs are typically underpowered to detect rare outcomes that may become apparent in larger and more broadly defined populations. Empagliflozin's safety has not been evaluated in a substantial real-world population for potential severe unintended adverse effects of SGLT-2i, including bone fractures, lower limb amputations (LLA), diabetic ketoacidosis (DKA), and acute kidney injury (AKI).

KEYWORDS

1. Type 2 Diabetes Mellitus.
2. SGLT2 inhibitors.
3. Empagliflozin.
4. Glycemic control.

ABBREVIATIONS

1. RCT - randomized controlled trials.
2. MetS - metabolic syndrome.
3. The EMPA-REG OUTCOME - Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus.
4. HHF - Hospitalisation for heart failure

SGLT-2i - sodium-glucose cotransporter 2

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INTRODUCTION

Diabetes presents a threat to global health. In 2015, diabetes ranked as the 15th main cause of years of life lost worldwide.[38] Its prevalence has risen rapidly over the past four decades, making it the 15th leading cause of life loss. Despite the World Health Organization's (WHO) objective to stop the rise in the prevalence of diabetes and the Sustainable Development Goal (SDG) to decrease premature mortality from non-communicable diseases (NCDs) by one-third by 2030, the outlook is not encouraging:[37] According to recent projections, there will be 642 million individuals with diabetes worldwide between the ages of 20 and 79 in 2040, up from 415 million in 2015 (1 in 11 adults).[39,43]

There are currently 135 million diabetics in the world, with India having the most (40.9 million in 2007). In addition, 80,9 million Indians are projected to have diabetes by 2025. The prevalence of diabetes among urban Indians has consistently increased from 2.1% in the 1970s to 8.2% in the 1980s and then to 12-16%.[16,17,18] Consequently, the documented high prevalence of diabetes among Asian Indian migrants has now extended to urban India and is rapidly spreading to rural India as well. In India, population-based statistics on the prevalence of coronary artery disease (CAD) are insufficient, particularly when comparing diabetic and nondiabetic individuals.[19]

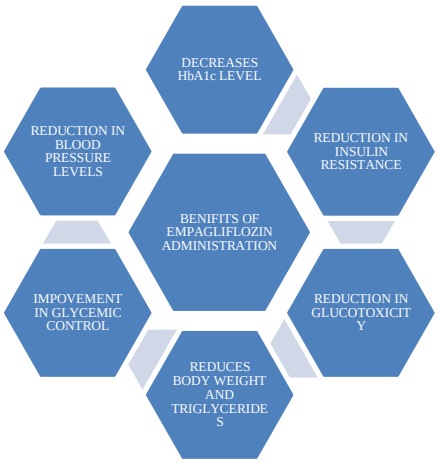

Figure 1:Benifits of empagliflozin administration

USFDA APPROVAL FOR EMPAGLIFLOZIN

Today, the US Food and Drug Administration approved Jardiance (empagliflozin) to reduce the risk of cardiovascular mortality and hospitalization for heart failure in adults.

In AUGUST 2014 FDA approved Jardianceas an adjunct to diet and exercise to improve glucose control in individuals with type 2 diabetes.[7] Jardiance has also been approved to reduce the risk of cardiovascular mortality and hospitalization in patients with heart failure and a low ejection fraction.[29]

MECHANISM OF ACTION OF EMPAGLIFLOZIN

Empagliflozin inhibits the sodium-glucose cotransporter 2 (SGLT2), the main transporter responsible for the reabsorption of glucose from the glomerular filtrate back into circulation. Empagliflozin increases urine glucose excretion by lowering the renal glucose threshold and decreasing renal glucose reabsorption. This is achieved by blocking SGLT2. In addition, empagliflozin increases sodium transport to the distal tubule and decreases salt reabsorption. This may influence a variety of physiological processes, including the reduction of pre- and

afterload on the heart and suppression of sympathetic activity.

ROLE OF EMPAGLIFLOZIN IN TYPE 2 DIABETES MELLITUS PATIENTS

Diabetes Mellitus (DM) is a multifactorial chronic disease that affects a significant portion of the population, and the World Health Organization (WHO) predicts that the number of adults living with diabetes will increase.[15] As type 2 diabetes mellitus (T2DM) affects the vast majority of diabetic patients (approximately 90-95%), mono-target treatment often fails to control blood glucose levels and other comorbidities.[14] Empagliflozin, an inhibitor of sodium-glucose cotransporter 2 (SGLT2), facilitates glycemic management in T2DM patients. Oral antidiabetics typically appear first when it comes to managing type 2 diabetes and modifying lifestyle. There are currently seven classes of anti-diabetic medications, and additional classes are under consideration. Included in these classifications are thiazolidinediones, biguanides, sulphonylureas, alpha-glucosidase inhibitors, GLP receptor agonists, DPP-4, and SGLT-2 inhibitors.[25] These substances are known as sodium-glucose co-transport (SGLT-2) inhibitors. SGLT-2 inhibitors treat diabetes by preventing the reabsorption of glucose from the proximal convoluted tubule of the kidney.[27] This effect results in an increase in glucose excretion via urine.[26] This review highlights the efficacy and safety profile of empagliflozin in patients with type 2 diabetes.

Hypoglycemia is a major concern among patients with T2DM.[32] In this extensive data set, empagliflozin was not associated with an increased risk of hypoglycemia compared to a placebo, except for individuals taking sulfonylurea as a background medication. Empagliflozin's insulin-independent mechanism of action would not be expected to increase the risk of hypoglycemia. However, sulfonylureas, which stimulate insulin secretion, are associated with an increased risk of hypoglycemia, and the use of additional SGLT2 inhibitors increases the risk of hypoglycemia.[24] When empagliflozin is combined with sulfonylurea or insulin, a reduced dose of the sulfonylurea or insulin should be considered to reduce the risk of hypoglycemia.[31]

ROLE OF EMPAGLIFLOZIN IN PATIENTS HAVING HYPERTENSION

Treatment with empagliflozin for 12 weeks significantly and clinically meaningfully improved 24-h SBP and DBP compared to placebo, which was accompanied by decreases in daily and night time BP, hourly mean ABPM, and office BP. Each 20 mmHg increase in SBP or 10 mmHg increase in DBP above the BP range of 115/75 to 185/115 mmHg doubles the risk of cardiovascular disease.[21] In randomized controlled trials, significant cardiovascular events in diabetic patients were reduced when their SBP was reduced to 150 mmHg and their DBP was reduced to 85 mmHg.[22] In patients with type 2 diabetes and hypertension, a treatment strategy that included BP and glycemia control substantially reduced the risk of cardiovascular complications and mortality.[23]

The occurrence of genitourinary infections has been documented as the most common negative effect of glycosuria.[35] The most common cause of these infections is genital mycosis; however, some studies have also documented bacterial urinary tract infections.[30,3] The possibility of volume depletion in the HF population due to the concomitant use of diuretics is less frequent but potentially more significant.[28]

Diabetic ketoacidosis was not more common in people given empagliflozin

compared to those given a placebo, according to a meta-analysis of clinical study data.[32] However, more people taking empagliflozin than those taking a placebo noted elevated ketone levels in their urine.[32,3]

CLINICAL INTERPRETATION

A reduction in HbA1c and FPG that was clinically and statistically significant was observed in the treatment group, indicating that EMPA is capable of managing glycemia both as a monotherapy and as an add-on therapy. (i.e., EMPA add-on to metformin, metformin plus sulfonylurea, metformin plus linagliptin, pioglitazone or pioglitazone plus metformin, linagliptin, and insulin with or without OAD). This is also strongly supported by the observation that a considerably greater proportion of patients achieved their glycemia target of HbA1c 7% than in the placebo group.[34] Similar reductions in HbA1c and FPG were observed between EMPA-treated and placebo-treated individuals with type 2 diabetes. The results lend additional support to the theory that SGLT2 antagonists could reduce glycemia by increasing the quantity of glucose excreted in the urine.

Second, glycosuria causes osmotic diuresis, which contributes to a decrease in body weight and blood pressure. These two advantages are attributable to glycosuria. Thirdly, clinical trials demonstrated that SGLT2 inhibitors can effectively transfer substrate utilization away from carbohydrates and towards lipids, resulting in a decrease in fat storage in type 2 diabetes patients.[36]

To determine the safety profile and tolerability of empagliflozin, the safety profile data from Phase I to III clinical trials involving more than 13,000 patients with type 2 diabetes were analyzed comprehensively. Patients who received empagliflozin did not have an increased risk of experiencing adverse events, including severe adverse events, significant adverse events, or adverse events that led to medication discontinuation.[2]

Compared to a placebo, empagliflozin did not increase the risk of hypoglycemia unless it was combined with sulfonylurea and/or basal insulin. Empagliflozin monotherapy would not be expected to be associated with an increased risk of hypoglycemia based on its mechanism of action, which is independent of the action of insulin. However, sulfonylureas are associated with an increased risk of hypoglycemia, and it has been reported that the risk of hypoglycemia increases when other anti-diabetes medications, such as other SGLT2 inhibitors, glucagon-like peptide-1 agonists29, and dipeptidyl peptidase-4 inhibitors, are combined with a sulfonylurea.[10,11] When empagliflozin is combined with sulfonylurea, the risk of hypoglycemia must be considered, and the sulfonylurea dose may need to be lowered. When insulin is used in conjunction with empagliflozin, it is recommended that insulin dosage be decreased to reduce the risk of hypoglycemia.[6]

Because they increase the quantity of glucose lost in the urine, SGLT2 inhibitors are associated with osmotic diuresis. Empagliflozin prescribing information acknowledges the possibility of volume depletion in more susceptible patients, including the elderly, those with renal impairment, those with low systolic blood pressure, and those taking diuretics. In this large data set, the incidence of volume-depleting events was comparable between empagliflozin and placebo; however, a higher incidence of volume-depleting events was observed in patients aged 75 years and in patients who were receiving loop diuretics at the beginning of the study. Empagliflozin-treated patients had a higher incidence of adverse events (AEs) such as pollakiuria than placebo-treated patients.[8]

In patients treated with empagliflozin, the incidence of events consistent with genital infection was higher than in patients treated with a placebo. Infrequently such occurrences necessitate or prolong hospitalization. With other SGLT2 inhibitors, an increased risk of genital infections, particularly in female patients, has also been reported. This was especially the case for patients receiving antibiotics. In this pooled analysis, the incidence of UTI-like events was comparable between empagliflozin- and placebo-treated patients. However, an increased risk of UTI-like events, particularly in female patients, was observed in some clinical trials and is acknowledged on the product label. In this instance, the incidence of UTI-like events was comparable between empagliflozin- and placebo-treated patients. Hospitalization for a protracted period or a few UTI-like symptoms is required.[30]

SUMMARY

The prevalence of metabolic syndrome continues to increase globally, making it a constant threat. Metabolic syndrome is characterized by elevated triglycerides, low HDL cholesterol, high blood pressure, central adiposity (belly obesity), and high blood sugar. (MetS). MetS significantly increases the risk of cardiovascular disease, cerebrovascular disease, kidney disease, liver disease, and other terrible outcomes. Patients with type 2 diabetes were able to safely consume doses of 10 and 25 mg of empagliflozin. In comparison to the placebo, empagliflozin doses of 10 or 25 mg were not associated with an increased incidence of UTI, bone fracture, malignancy, decreased renal function, or DKA. Empagliflozin was not associated with a higher rate of hypoglycemic events compared to placebo, except in patients taking sulfonylureas and/or insulin on a background basis. In the empagliflozin group, more cases of genital infection-like events occurred than in the placebo group. Empagliflozin 25 mg was associated with a higher incidence of adverse events consistent with volume depletion in patients aged >75 years compared to placebo. Except for an increase in genital infections, EMPA therapy was largely well tolerated in patients with type 2 diabetes. Among those who would benefit most from obtaining EMPA are patients with type 2 diabetes who are overweight or at risk for weight gain. Combining EMPA with metformin, metformin plus sulfonylurea, metformin plus linagliptin, metformin plus pioglitazone, insulin with or without an OAD, or insulin plus linagliptin is recommended. However, additional research is required to explicitly compare EMPA to a placebo, both as a standalone treatment and in conjunction with other antidiabetes drugs.

CONFLICT OF INTEREST

The authors have stated that they do not have any competing or conflicting interests that would prevent them from publishing this article.

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